diabetic PAI-1 +/+ mice, is weak when compared with nondiabetic mice (×1.5), and is hardly distinguishable from the induction observed in PAI-1 −/− mice, at least for the eye (Fig. 3). Another striking result is that the level of TGF-beta expression and production by the kidney is higher in PAI-1 −/− mice than in PAI-1 +/+ mice, in either basal or diabetic conditions. In the absence of pathologic data, including measurements of the glomerular basement membrane thickness, it is therefore difficult to conclude that PAI-1 knockout animals could be protected towards diabetic nephropathy and that this would be related to a lower concentration of TGF-beta.

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Reply from the Authors

As we gain further insight into PAI-1–mediated mechanisms in disease, it is evident that PAI-1 may indeed have several functions. Early studies showed that PAI-1 deficiency protects against fibrosis, as in the bleomycin-induced pulmonary model [1], and this is supported by our studies in the streptozotocin-induced diabetic mouse model [2].

However, Hertig and Rondeau demonstrate that in inflammatory models of disease, PAI-1 deficiency may promote pathology. In fact, we have observed development of cardiac fibrosis in PAI-1−/− mice (unpublished data), as have Moriwaki et al [3], who also showed significant macrophage involvement in this process. These observations strongly suggest that PAI-1 function may be determined by the inciting process, and modulated by uPA expression, which may be tissue- or disease-specific.

The comment that induction of TGF-β synthesis is weak (1.5 ×'s) reflects similar changes in total TGF-β by Hertig et al (1.9 ×'s) [4]. Active TGF-β was not measured in our paper. As such, it is provocative to assume that a seemingly "weak" stimulation of TGF-β protein by PAI-1 may not have a significant clinical outcome (i.e., worsened albuminuria). Our data showed no significant difference in basal kidney TGF-β expression, which was significantly reduced in diabetic PAI-1−/− mice (Fig. 3).

Significant structural changes of diabetic nephropathy, such as glomerular basement membrane thickness and fractional mesangial volume, are not typically observed after 4 weeks of diabetes in C57BL6 STZ-induced diabetic mice and, in fact, may not appear until ∼6 months of diabetes. For this reason, these parameters were not included in our study.

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Does fluvastatin really have an antioxidant effect in humans?

To the Editor: In the recent issue of *Kidney International*, Pat et al demonstrated that renal fibrosis after unilateral ureteral obstruction in rat was attenuated by the antioxidative effect of fluvastatin [1], a HMG-CoA reductase inhibitor notable for its additional antioxidant effect [2]. We undertook this clinical experiment because no in vivo human data are available addressing the antioxidant effect of fluvastatin. The patients studied consisted of 3 males and 3 females, with an average age of 56.5 years. All had biopsy-proven chronic glomerulonephritis with normal ranges of creatinine clearance and serum total protein. The mean urinary protein excretion was